

## The effect of coronavirus infection (COVID19) on fetomaternal blood flow at term

Coronavirus infection during pregnancy

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### Abstract

**Aim:** The aim of this study is to evaluate maternal and fetal blood flow parameters of term pregnant women who had recovered from COVID-19 during pregnancy.

**Material and Methods:** The study was conducted on 100 term pregnant women followed at the Department of Obstetrics and Gynecology, University of Health Sciences, Erzurum Regional Training and Research Hospital, Erzurum, Turkey. All of these pregnant women agreed to participate in the study. Two groups were formed. Patients with a term pregnancy who had a positive reverse transcription-polymerase chain reaction for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection at any week of pregnancy, who later recovered, were included in the study group (Group 1). The control group (Group 2) consisted of 50 healthy term pregnant women. Smokers, alcohol users, multiple pregnancies, complicated pregnancies (such as preeclampsia, fetal malformation, gestational diabetes, placenta previa), and those with a pregnancy below 37 weeks were not included. First, a routine ultrasound examination was performed on all pregnant women. Then, the umbilical artery, uterine artery, and middle cerebral artery pulsatility index (PI), resistance index (RI), and systole/diastole ratios (S/D) were recorded using Doppler ultrasonography. Obtained data and results were compared between groups using the independent T-test.

**Results:** Demographic characteristics of the groups were similar. There was no difference between the groups in terms of maternal and fetal blood flow parameters.

**Discussion:** In this current study, fetal and maternal blood flow parameters of term pregnant women who recovered and did not have coronavirus infection during pregnancy were compared. The uterine, umbilical and mid cerebral artery blood flow parameters of the participants were observed to be similar.

### Keywords

COVID-19, Doppler Ultrasound, Middle Cerebral Artery, Pregnancy, Umbilical Artery, Uterine Artery

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This study was approved by the Ethics Committee of University of Health Sciences, Erzurum Regional Training and Research Hospital (Date: 2021-03-01, No: 2021/05-115)

## Introduction

After the World Health Organization declared COVID-19 a pandemic, various studies were carried out, especially its effect on pregnant women and fetuses [1-4]. The virus, which infected more than 529 million people all over the world, caused the death of more than 6 million people [2]. Naturally, it also affected pregnant women [3]. Although frequency of vertical transmission the disease to the fetus has not been determined, it has been determined to cause severe acute respiratory failure and adversely affect fetal perfusion [4]. Although there were high concerns about the effect on the fetus at the beginning of the pandemic, it has been determined that fetal side effects were not so much with increasing clinical experience [5].

Doppler ultrasound detects changes in circulating blood flow patterns. Risky conditions for the fetus may be detected via fetal Doppler ultrasound and it has been reported to be effective to evaluate high-risk pregnancies [6]. Umbilical artery (UA) Doppler is accepted as an important surveillance tool in fetal growth retardation [7]. In chronic hypoxia, cerebral vasodilation occurs; cerebral diastolic flow increases, and Doppler indexes of the Middle cerebral artery (MCA) decrease to protect the brain [8]. Researchers reported that the MCA Doppler may be a good tool for detecting risky fetuses [9]. Uterine artery (UtA) Doppler velocimetry evaluation is a non-invasive approach that reflects the degree of placental perfusion. It reflects the remodeling of the incomplete spiral arteries, which is responsible for preeclampsia [10]. UtA Doppler parameters have been reported to be associated with maternal cardiovascular function [11].

One of the most important purposes of prenatal Doppler ultrasonography is to detect fetuses with a high risk for perinatal morbidity and mortality. The aim of the study is to evaluate the maternal and fetal blood flow parameters of term pregnant women who recovered from COVID-19 during pregnancy, to investigate the effects of COVID-19 infection during pregnancy on these parameters and to reveal the negative effects if any.

## Material and Methods

For this prospective case-control study, permission was obtained from the Ethics Committee of the University of Health Sciences, Erzurum Regional Training and Research Hospital (No: 2021/05-115). The study was carried out with 100 pregnant women aged 20-40 years who were followed up at the Obstetrics and Gynecology Clinic, University of Health Sciences, Erzurum Regional Training and Research Hospital, Erzurum, Turkey. All pregnant women agreed to participate in the study and signed informed consent was obtained from all participants. Two groups were formed (n=50 in each group). Patients with a term pregnancy who had a positive reverse transcription-polymerase chain reaction in nasopharyngeal and oropharyngeal samples for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in any week of pregnancy, who later recovered, were included in the study group (Group 1). The control group (Group 2) consisted of 50 healthy term pregnant women. Smokers, alcohol users, multiple pregnancies, complicated pregnancies (such as preeclampsia, fetal malformation, gestational diabetes, placenta previa), and those with a pregnancy below 37 weeks were not included in the study. Age, weight, height, gravida, parity, vital signs,

biochemical analysis results, gestational week, and pregnancy week of the participants who recovered from COVID-19 were recorded. Fetal ultrasound examination was performed by two obstetricians (A.N.A and B.A.) transabdominally using the LOGIQ F8 expert GE Healthcare ultrasound system (with a 3.5 M-Hz convex probe). Measurements were made when the fetus was immobile and there were no uterine contractions. Routine ultrasonography examination was performed on all pregnant women using Hadlock formula [12]. The amniotic fluid index value and biometric measurements, including biparietal diameter, abdominal circumference, and femur length were recorded. Then, the pulsatility index (PI), resistance index (RI), and systole/diastole ratios (S/D) of the umbilical, uterine, and middle cerebral arteries were recorded with Doppler Ultrasonography. The UtA was visualized distal to the area where the iliac artery is on both sides. The UA was examined over the free loop of the umbilical cord and MCA was visualized in the transverse axial position of the fetal head. All flow measures were made according to color Doppler Ultrasonography standard protocol [13,14].

## Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS.22; IBM SPSS Statistics for Windows, Version 22.0). Data were shown as means  $\pm$  error standards or numbers. The normality of variables was tested with the Kolmogorov-Smirnov test. Flow parameters between groups were compared using the Independent T-test. Pearson's correlation analysis was performed to investigate the correlation between the gestational week of coronavirus infection and Doppler parameters. P-value <0.05 was considered statistically significant.

## Ethical Approval

Ethics Committee approval for the study was obtained.

## Results

During the study period, 80 pregnant women were diagnosed with COVID-19 and completed the quarantine process. Twenty patients had comorbidities such as diabetes, chronic hypertension, and high body mass index, and 60 patients met inclusion criteria. Fifty pregnant women agreed to participate in the study. Eventually, the data of 50 participants for the study

**Table 1.** Comparison of groups in terms of demographic characteristics.

	Group 1 (n=50)	Group 2 (n=50)	P-value
Age (years)	29.47 $\pm$ 4.23	29.80 $\pm$ 4.92	0.719
Height (cm)	163.10 $\pm$ 4.65	162.96 $\pm$ 5.39	0.891
Weight (kg)	75.99 $\pm$ 9.20	75.76 $\pm$ 9.87	0.904
Gestational week	37.73 $\pm$ 0.69	37.74 $\pm$ 0.85	0.925
Gravidity	2.14 $\pm$ 1.00	2.32 $\pm$ 1.47	0.468
Mean arterial pressure (mmHg)	83.50 $\pm$ 4.48	82.20 $\pm$ 3.36	0.101
Heart rate (bpm)	83.71 $\pm$ 3.18	84.52 $\pm$ 3.17	0.201
Weight gain during pregnancy	9.77 $\pm$ 3.44	10.68 $\pm$ 3.60	0.200
Amniotic fluid index	74.12 $\pm$ 12.95	71.10 $\pm$ 16.60	0.310
Estimated fetal weight (gram)	2632.72 $\pm$ 552.56	2735.52 $\pm$ 600.22	0.375

Group 1: Patients who had COVID-19 infection during pregnancy

Group 2: Patients who have not been infected with COVID-19 during pregnancy

**Table 2.** Comparison of maternal and fetal blood flow parameters of the groups.

	Group 1 (n=50)	Group 2 (n=50)	P-value
UtA PI	1.68 ± 1.48	1.27 ± 1.45	0.167
UtA RI	0.65 ± 0.33	0.61 ± 0.29	0.504
UtA S/D	2.48 ± 1.70	2.14 ± 0.77	0.194
UA PI	1.19 ± 1.33	1.19 ± 1.93	0.985
UA RI	0.59 ± 0.28	0.61 ± 0.30	0.666
UA S/D	2.44 ± 0.75	2.51 ± 0.74	0.643
MCA PI	1.67 ± 1.47	1.61 ± 1.30	0.830
MCA RI	0.69 ± 0.16	0.75 ± 0.17	0.104
MCA S/D	4.13 ± 2.96	4.68 ± 2.54	0.324

Group 1: Patients who had recovered from COVID-19 infection during pregnancy

Group 2: Patients who have not been infected with COVID-19 during pregnancy

UA: Umbilical artery, MCA: Middle cerebral artery, UtA: Uterine artery.

group were analyzed. Fifty term pregnant women with similar demographic characteristics, who did not have COVID-19 during pregnancy, were matched as the control group. The demographic characteristics of the groups were similar (Table 1).

The ages of the pregnant women were between 20-40 years. Among women who were positive for SARS CoV-2, 10 (20%) were asymptomatic and 40 (80%) were symptomatic, all of whom had mild clinical manifestations, including cough, anosmia, fever, diarrhea, runny nose, nasal congestion, and fatigue. None of the patients required intensive care and steroid treatment. There was no difference between the groups in terms of maternal and fetal blood flow parameters (Table 2). No correlation was observed between study parameters.

## Discussion

Fetal Doppler ultrasonography is a very common tool to detect fetal well-being in the last trimester. Doppler measurements are used in case of fetal growth restriction and the follow-up of high-risk pregnancies [15]. Differences between peak systolic and end-diastolic flow rates in each cardiac cycle indicate reverse flow caused by vascular resistance [16]. Researchers suggested that maternal COVID-19 may affect the oxygen supply of the fetus, leading to placental insufficiency, IUGR, fetal distress, and fetal death [17]. In the current study, fetal and maternal blood flow parameters of term pregnant women who recovered and did not have coronavirus infection during pregnancy were compared. The uterine, umbilical and mid cerebral artery blood flow parameters of the participants were observed to be similar.

The UtA Doppler is more valuable in the third trimester. Recent findings show that third-trimester UtA Doppler is important in determining the risk of stillbirth and perinatal death [18]. Fetal MCA Doppler PI is used to evaluate fetal oxygenation. Reduction in MCA impedance has been shown to be associated with fetal hypoxemia and acidemia [19]. Mok et al. [20] reported abnormal neonatal outcomes in pregnant women infected with Zika viruses. They observed low peak systolic velocity measurements of MCA in these patients and they concluded that the MCA blood flow parameter may provide clinical benefit in the surveillance of pregnant women affected by Zika viruses. In the study by Karlsen et al. [21] they evaluated the PI value of MCA to prevent poor perinatal outcomes, and reported a

significant correlation between MCA PI and adverse perinatal outcomes in high-risk populations. In the current study, no significant differences were found in terms of PI and RI values of MCA between term pregnant women who had COVID-19 during pregnancy and those who did not [22].

During the COVID-19 pandemic, clinicians investigated the relationship between the SARS-CoV-2 infection during pregnancy and adverse maternal and perinatal outcomes. In a recent Canadian surveillance study, 6012 pregnant individuals with SARS-CoV-2 were analyzed [23]. This exploratory surveillance study reported a significant association between SARS-CoV-2 infection during pregnancy and adverse maternal outcomes and preterm birth. In another study, five cases of fetal death, which occurred in patients with relatively mild forms of COVID-19 were reported [23]. In all five cases, placental histology had acute chorioamnionitis. In the current study, intrauterine fetal death was not detected in any of the continuing pregnancies that have recovered from maternal SARS-CoV-2 infection. Also, fetomaternal blood flow parameters in these patients were similar to the patients who have not had COVID-19. Consistent with our results, Soto-Torres et al. [24] found no significant differences in fetal ultrasound and Doppler findings between pregnant women who were positive for SARS-CoV-2 and those who were negative. But unlike our results, they reported more frequent deliveries  $\leq 35$  weeks among SARS-CoV-2-positive women compared to controls. Unlike their study, patients with comorbidities were not included in this current study. They included all SARS-CoV-2-positive women in their retrospective case-control study. In another study, Anuk et al. [25] compared maternal-fetal Doppler patterns in pregnant women who were diagnosed with COVID-19 and completed the quarantine period with healthy pregnant women. They reported higher pulsatility and resistance indices of UA and UtA in pregnant women who recovered from COVID-19 compared to the control group. Inconsistent with their results, we observed no significant differences between term pregnant women who recovered from COVID-19 and controls in terms of fetomaternal Doppler flow parameters. The reason for these different results may be related to the methodological differences in the studies. Anuk et al. [25] performed Doppler measurements during the week of pregnancy who had COVID-19 disease and completed the quarantine period. Whereas, we performed all Doppler ultrasound evaluations at term. We recorded the pregnant women who were diagnosed with COVID-19, followed up, and performed Doppler ultrasound and fetal biometry measurements when they reached 37 and above gestational weeks. This is the first study to investigate fetomaternal Doppler parameters in term pregnant women with recovered from COVID-19 infection. We reported that fetomaternal blood flow parameters similar in pregnant women who recovered from COVID-19 infection to healthy pregnant women.

## Limitations

The limitation of this study was the lack of information about the long-term follow-up of the participants such as mode of delivery, and APGAR scores of the baby. However, the aim of this current study was to evaluate the effect of COVID-19 infection during pregnancy on fetomaternal blood flow parameters at term.

## Conclusion

In conclusion, this present study reported no significant differences in fetomaternal blood flow parameters in term pregnant women who recovered from COVID-19 during pregnancy compared to those who have not had the disease. Further studies are required to investigate the association between the gestational age at the time of diagnosis of COVID-19 and placental perfusion at term.

## Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

## Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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## Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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